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TOPICAL FILM FORMING SPRAY FORMULATIONS OF S-IBUPROFEN

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Abstract: Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have an emerging role in the treatment of certain types of acute pain. In addition to their convenience, efficacy and safety, they are an attractive option, particularly when considering current concerns about the safety of cyclooxygenase-2 (COX-2) inhibitors (coxibs). The pharmacologically effective dose is delivered at the site of pain, so there is minimal systemic absorption and thus low risk of related adverse effects. Topical NSAIDs provide a therapeutic option for treatment of acute, localized, soft tissue injuries or painful conditions in different areas of the body. The objective of the present work was to develop metered dose spray formulations for topical delivery of NSAIDs by varying type and content of the film forming polymers (various grades of Eudragits) as well as nature and content of the plasticizer. Spray solutions were prepared using Ethanol:Acetone as solvent system and Eudragits S-100, E-100, RLPO as film forming polymer. Combination of camphor and menthol were used as permeation enhancer. Topical sprays formulations offer improved patient compliance by sustaining the action and also avoid gastrointestinal side effects. Formulated Topical sprays were evaluated for pH, clarity of solution, spray pattern, spray angle, dermal adhesion of film, flexibility of film, water was hability of film, volume of solution delivered upon each actuation (or per spray), drug content per spray, film formation time, in vitro drug transport and retention. Diffusion studies of the optimized formulation through the freshly excised porcine skin showed controlled release of drug over a period of 24 hours indicating that the formulations will provide a sustained topical delivery of NSAIDs. A skin irritation study was also carried out using rat as an animal model. Anti-Nociceptive activity was performed on Albino Wistar rats for determination of anti-inflammatory and analgesic activity of the developed formulations. Thus, film forming sprays provide promising and innovative therapeutic systems and will be advantageous over currently available conventional gels, creams and patches.

Keywords: NSAIDs, Metered dose spray.

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INTRODUCTION

Ibuprofen [2-(4-isobutylphenyl)propionic acid], a potent non-steroidal anti-inflammatory (NSAID) drug that is often used for the treatment of acute and chronic arthritic conditions, has pH dependent solubility and permeability (Mizumoto, 2005). S(+)Ibuprofen is the active dextrorotatory enantiomer of Ibuprofen. It is a nonselective inhibitor of Cyclo-oxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. S-Ibuprofen (Dexibuprofen) has been proven to be its active form by both in-vitro and in-vivo studies. The advantages of S(+)Ibuprofen include greater clinical efficacy, ease in dose optimization, less variability in therapeutic effects, all of these at half the dose of Ibuprofen.

Generally the formulations of Dexibuprofen commercially available are in oral dosage forms. Therefore, there is a need to develop topical or other dosage forms of S(+)Ibuprofen to minimize the gastrointestinal side-effects of oral Dexibuprofen, and to provide relatively consistent drug levels at the application site for prolonged periods (Prausnitz MR, 2008).

A recent development that attempts to overcome some of the limitations of TDD systems involves application of the concept of evaporative delivery and formulating aerosol sprays.

“The metered dose topical spray is a solution (Topical Aerosol) made up of a volatile and non-volatile vehicle containing drug dissolved as single phase solution.”(Finnin B.C., 2002) The volatile components of the vehicle evaporate, leaving the remaining non-volatile penetration enhancers and drug to rapidly partition into the stratum corneum. This system after drying results in a stratum corneum reservoir made up of the drug and enhancer. MDTS,are quick drying and non-occlusive, offer a better alternative to both the patch and gel systems for easy application and better tolerance. Moreover, the spray can form a “patchless drug reservoir” on the skin (Leichtnam ML, 2006).

2. MATERIALS AND METHODS:

2.1 Materials:

Dexibuprofen was obtained as a gift sample from Shasun pharmaceuticals Pvt. Ltd, India. Polyacrylic resins (Eudragits RLPO, Eudragits RL-100, Eudragit E-100 and Eudragit S-100) were procured from Evonik Degussa Pvt. Ltd. (Mumbai, India). PEG 400, Propylene glycol (PG), ethanol and acetone were purchased from S.D Fine Chemicals Pvt., Ltd. (Mumbai). Camphor and menthol were purchased from Sigma Aldrich (Mumbai). The other chemicals and reagents were of analytical grade. All the animals used in this study were procured from Bharat Serums Pvt. Ltd, Thane.
2.2 Preparation of metered dose topical spray solutions:

First the polymeric solvent system was made by incorporating polymers into the ¾th quantity of solvent system used. The polymer gets solubilized in this polymeric system quickly. Drug was allowed to dissolve in the mixture of remaining solvent system and plasticizer. Once the drug was completely dissolved, polymeric solvent system was added to the drug solution. Total weight of this system was adjusted with the solvent system in such a way that desired amount of drug could be obtained after each actuation.

2.3 Optimization of excipients concentration for topical spray formulations:

Optimization of sprays involved selection and investigation of optimum concentrations of polymer, solvent system, penetration enhancers and pH of the sprays so as to get enhanced drug penetration, reduced irritation as well as minimum side effects.

2.3.1 Selection of solvent/s and optimization of their concentration:

Dexibuprofen is insoluble in water. It is soluble in organic solvents like Ethanol, Acetone and Isopropyl Alcohol. Ethanol and acetone were attempted as solvents in concentration of 40–65% as they are the most common solvents used in topical drug delivery systems and are capable of extracting stratum corneum lipids (Warren R; 1989).

2.3.2 Optimization of polymer and its concentration:

Eudragit RS100, Eudragit E100, Eudragit RLPO, Eudragit S-100 and PVP K-30 were selected for investigation of their capacity for spray formation. These film forming polymers were used at various concentrations. The optimum polymer was selected based on the physical characteristics of the film. Our aim was to achieve a clear, transparent, quick-drying and water-washable film.

Table 1: Preparation of Spray formulations using varying concentration of polymers.

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>FORMULATION CODE (Quantity in % w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1 S2 S3 S4 S5 S6 S7 S8 S9 S10 S11 S12</td>
</tr>
<tr>
<td>Dexibuprofen</td>
<td>10 10 10 10 10 10 10 10 10 10 10 10</td>
</tr>
<tr>
<td>Eudragit RS100</td>
<td>2.5 5.0 - - - - - - - -</td>
</tr>
<tr>
<td>Eudragit RLPO</td>
<td>- - 2.5 5.0 7.5 - - - - - -</td>
</tr>
<tr>
<td>Eudragit S100</td>
<td>- - - - 2.5 5.0 - - - - - -</td>
</tr>
<tr>
<td>Eudragit E100</td>
<td>- - - - - - 2.5 5.0 7.5 - -</td>
</tr>
<tr>
<td>PVP K30</td>
<td>- - - - - - - - 2.5 5.0 7.5  - -</td>
</tr>
<tr>
<td>Ethanol:</td>
<td></td>
</tr>
<tr>
<td>Acetone (8:2) to</td>
<td></td>
</tr>
<tr>
<td>make volume 100%</td>
<td></td>
</tr>
<tr>
<td>Q. S 100 %</td>
<td></td>
</tr>
</tbody>
</table>

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2.3.3 Selection of plasticizers and optimization of their concentrations:

Plasticizers play an important role in formation of an acceptable film forming spray. Various plasticizers such as PEG 400, Propylene glycol and Dibutyl Phthalate were used at concentrations of 0.25-1.0 % and their effect on % drug permeated and topical flux was investigated.

Table 2: Preparation of Spray formulations using varying concentrations of plasticizers.

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>FORMULATION CODE (Quantity in % w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$S_{13}$</td>
</tr>
<tr>
<td>Dexibuprofen</td>
<td>10</td>
</tr>
<tr>
<td>Eudragit RLPO</td>
<td>2.5</td>
</tr>
<tr>
<td>PEG 400</td>
<td>0.25</td>
</tr>
<tr>
<td>Dibutyl Phthalate</td>
<td>-</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>-</td>
</tr>
<tr>
<td>Ethanol: Acetone</td>
<td>-</td>
</tr>
</tbody>
</table>

2.3.4 Selection of penetration enhancers and optimization of their concentration:

Penetration enhancers such as Camphor, Menthol and Transcutol P were explored in the concentration 0.5 % w/w in the formulation of metered dose topical spray formulations of Dexibuprofen 10 % as depicted in Table 3. The effect of concentration of penetration enhancers was observed on flux, permeability co-efficient and % drug permeated at the end of 24 hours.

Table 3: Preparation of Spray formulations using varying concentration of penetration enhancers.

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>FORMULATION CODE (Quantity in % w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$S_{19}$</td>
</tr>
<tr>
<td>Dexibuprofen</td>
<td>10</td>
</tr>
<tr>
<td>Eudragit RLPO</td>
<td>2.5</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>0.25</td>
</tr>
<tr>
<td>Menthol</td>
<td>0.5</td>
</tr>
<tr>
<td>Camphor</td>
<td>-</td>
</tr>
<tr>
<td>Transcutol P</td>
<td>-</td>
</tr>
<tr>
<td>Ethanol: Acetone</td>
<td>-</td>
</tr>
</tbody>
</table>

(8:2) to make volume 100%
2.4 Selection of Containers:

The present study utilized APF<sup>Plus</sup> (Advance preservative free) screw-on spray container from Aptarpharma for delivering the accurate amount of drug from container.

2.5 Evaluation of Optimized Spray Formulations:

The metered dose topical spray formulations were evaluated on the basis of tests indicated for aerosol preparations as per monographs in IP, BP and USP.

2.5.1 <i>in-vitro</i> Permeation Study

Procedure: - <i>In-vitro</i> diffusion study was conducted using horizontal static Franz-diffusion cells with receptor volume 20 ml and diffusional area of 3.14cm<sup>2</sup>. Dialysis membrane was used as a diffusion membrane and was placed between the donor and the receptor compartments of the Franz-diffusion cell. Aliquots (2 ml) of receptor medium were withdrawn and replaced with fresh medium at specified intervals of time i.e. 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours and analysed by UV spectrophotometer at wavelength of 263 nm. From this, % drug diffused was calculated and plotted against time (Fig.4).

2.5.2 <i>ex-vivo</i> Permeation Study

Procedure: - Membranes were separated from full thickness of skin removed from the surface of the ear of the pigs. Adhering fat and other visceral debris were removed carefully from the skin using tweezers. The freshly excised porcine skin was sandwiched between the donor and the receptor compartment of the Franz-diffusion cell with the stratum corneum facing the donor compartment.

After stabilization of the skin, diffusion studies on porcine skin were initiated. Diffusion studies were carried out on the sprays formulated using Eudragit RLPO as film forming polymer. The donor compartment facing porcine skin was loaded with 0.2ml of the spray solution. At specified intervals of time i.e. 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours, 2 ml aliquots were withdrawn from receptor compartment through the sampling port and it was replaced with the same amount of freshly prepared phosphate buffer pH 6.8 each time. Aliquots were analysed by UV spectrophotometer at wavelength of 263 nm. From this, % drug diffused at each time point was calculated and plotted against time (Fig.5).

2.5.3 Viscosity:

The viscosity of the solutions was measured at 25±1°C using Brookfield viscometer.
2.5.4 Volume of solution delivered upon each actuation:

The volume of solution delivered upon each actuation was calculated using eq. 1.

\[ AL = \frac{(Wt – Wo)}{Dn} \]  

Where AL is the volume of solution delivered upon each actuation, Wt is weight of formulation after actuation, Wo is the initial weight of the formulation before actuation, and Dn is the density of the formulation. An average weight of five actuations was calculated.

2.5.5 Spray angle:

Sudan red (10 mg) was dissolved in formulation to facilitate visualization. The sprays were actuated in horizontal direction onto a white paper mounted at a distance of 15 cm from the nozzle. The radius of the circle, formed on the paper, was recorded in triplicate from different directions. Spray angle (\( \theta \)) was calculated by eq. 2.

\[ \text{Spray angle} (\theta) = \tan^{-1} \left( \frac{l}{r} \right) \]  

Where ‘l’ is the distance of paper from the nozzle, and r is the average radius of the circle.

2.5.6 Spray Pattern:

Spray pattern of the metered dose topical spray formulations was checked by incorporating dilute solution of methylene blue in the formulation and spraying on Whatmann paper placed at a definite distance (Bakshi A; 2008). This paper was clipped on a board and the spray formulations were sprayed at the distance of 15cm.

2.5.7 Evaporation time/ Film formation time:

The evaporation time or time required for the spray film to dry was recorded. Time required for getting the completely dry film was checked.

2.5.8 pH:

The pH of the metered dose topical spray formulations was recorded by pH meter.

2.5.9 Drug content per spray:

The Drug content per spray was determined by actuating designed sprays in a beaker containing methanol. Then the drug content was analyzed by UV.
2.5.10 *Ex-in vivo* Physical Evaluation:

Placebo batches were actuated on left hand palms of three healthy human volunteers of 21–27 years in age, four times every 10 s from a distance of 15 cm. Time required for film formation, appearance of film, flexibility of film, feeling of warmth and subsequent cooling sensation, irritation potential and water washability were recorded.

2.6 Stability Studies on Developed Topical Formulations:

Stability studies on optimized topical spray formulations were conducted for a period of three months. The samples were kept at the following conditions as per ICH guidelines:

- 8°C ± 2°C
- 25°C ± 2°C / 60 ± 5 % RH
- 40°C ± 2°C / 75 ± 5 % RH

The samples were withdrawn periodically at time intervals of 0, 1\textsuperscript{st}, 2\textsuperscript{nd} and 3\textsuperscript{rd} month and evaluated for various physicochemical parameters.

2.7. Preclinical studies:

Animals were individually housed in cages for rats. Care of animals was taken according to the recommendations of Laboratory Animal Facility Guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India.

Lighting: 12 hours light / 12 hours dark cycles at Animal placement facility.

Room Temperature: 20°C ± 5°C

Relative Humidity: 30 to 50% Food: All animals had access to rat feed.

Water: Tap water was available *ad libitum*, to each animal via an automatic watering device. Study animals were acclimated to their housing for a minimum of 5 days prior to their first day of dosing.

2.7.1 Anti-inflammatory activity by carageenan induced paw edema:

Test Procedure:

Wister rats were divided into 3 groups with 5 rats in each group as given in Table.4. Rats were weighed and marks were made on left hind paw behind tibiatarsal junction. Pleurisy was
induced by injecting 0.1 ml of 1% w/v carrageenan solution subcutaneously into the sub-plantar surface of the left paw of the rat. 2 actuations of film forming spray formulations or the reference formulations were gently rubbed onto the plantar surface of the left hind paw 10 times with the index finger. The inflammatory response was assessed by measuring the thickness of the paw at 0.5, 2, 4, 6, 8, 10 and 24 hrs after carrageenan administration, using Vernier Calipers. The percentage of inhibition of edema was calculated using following formula.

**Formula:**

Paw thickness (mm) after carrageenan administration – paw thickness after particular time (mm) *100

Paw thickness after carrageenan administration (mm).

<table>
<thead>
<tr>
<th>Group</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control</td>
</tr>
<tr>
<td>II</td>
<td>Std (Volini spray)</td>
</tr>
<tr>
<td>III</td>
<td>Sample (Topical spray)</td>
</tr>
</tbody>
</table>

**Table. 4: Measurement of Inflammatory Response.**

2.7.2 Anti-nociceptive activity by Hot Plate method:

**Test Procedure:**

Animals were brought to test room; their body weights were recorded and were allowed to acclimate for 15 to 30 mins. Rats were placed into a 20 cm wide glass square on a hot plate maintained at 55 ºC. The rats were grouped into three, each group contained five rats each in order to reduce chances of variability and obtain a good statistical co-relation. Control latency was determined for each rat. The reaction time was recorded when animals jumped or licked their paws. Group I served as control. Group II was treated with 2 actuations of std Volini Spray. Group III was treated with 2 actuations of film forming topical spray. The animals were observed for nociceptive response (e.g. withdrawing or shaking or licking of a paw, or escape attempts by jumping) and the cutoff time was reached time was noted. A cut-off latency of 10 sec was employed to avoid any tissue damage. To determine a compound’s % MPE, a baseline measure was obtained for each animal prior to treatment with vehicle or test compound. Animal was then removed from the hot plate. The test was repeated after 0.5, 1, 2, 4 and 8 hrs. In order to analyze dose-effect relationships, the data were converted to % Maximal Possible Effect (% MPE) by the formula:

% MPE = 100 x (test latency – basal latency) / (cutoff time of 10 sec – basal latency).
Where, test latency is the latency to respond after treatment;

Baseline latency is the latency to respond prior to treatment; and

Cutoff time is the preset time at which the test will be ended in the absence of a response.

2.7.3 Skin irritation studies:

The Draize patch test was carried out using rats as the animal model (Agner Tove, 1990). The optimized formulation was sprayed on the patch of shaven skin and occluded with adhesive tapes and there resulting reactions such as erythema and edema were scored after 24 and 72h.

3. RESULTS AND DISCUSSION:

3.1 Preparation of metered dose topical spray solutions:

Metered dose topical spray solutions were prepared using a simple manufacturing process as described in section 2.2. Dextibuprofen in the concentration of 10% w/w along with polymers and plasticizers in varying concentrations were incorporated in the spray solutions.

3.2 Formulation and Optimization of Metered dose topical spray of Dextibuprofen:

3.2.1 Selection of solvent/s and optimization of their concentration:

Ethanol and acetone were used in combination in the ratio of 80:20 v/v in the formulation of metered dose topical spray of Dextibuprofen. Ethanol gave clear and homogenous solution of the drug. Acetone was used along with ethanol in the vehicle blend due to its ability to evaporate rapidly on application and thus to facilitate faster film formation (<8 min) on skin.

3.2.2 Selection of optimum polymer and its concentration:

Polymers such as Eudragit RS-100, Eudragit E-100, Eudragit RLPO, Eudragit S-100 and PVP K-30 were selected for investigation of spray formation. These film forming polymers were used at varying concentrations of 2.5%, 5.0% and 7.5% by its weight and various batches were formulated as mentioned in Table 1. Spray formulations S3, S4 and S5 formulated using 2.5%, 5.0% and 7.5% w/w of Eudragit RLPO produced acceptable films and they were transparent, non-tacky, not blowing and fast drying films and exhibited spherical spray pattern. Formulations S8, S9, and S10 formulated using Eudragit E-100 at concentration of 2.5%, 5.0% and 7.5% w/w respectively showed similar results. Formulations S1 and S2 formulated using Eudragit RS-100 at 2.5% and 5.0% concentration, S6 and S7 formulated using Eudragit S-100 at 2.5% and 5.0% concentration and formulation S11 and S12 formulated using PVP K30 at 2.5% and 5% concentration gave either fast blowing films with irregular spray patterns or whitish film on
appearance or sticky, slow drying films. Such films were undesirable and hence these formulations were not further evaluated.

3.2.3 Investigating the Effect of Polymer concentration on Drug Release

![Graph showing drug permeation profiles of formulations S3-S5, S8-S10:](image)

**Fig. 1: In vitro Drug Permeation Profiles of Formulation S3-S5, S8-S10:**

Effect of Eudragit RLPO and Eudragit E-100 at concentration of 2.5%, 5% and 7.5% on % drug permeated from the metered dose sprays was investigated. The % drug permeated ranged from 62.14% to 83.45% for formulations S3-S5 and S8-S10 which was low as compared to formulation S3. Amongst the formulations studied, the highest % drug diffusion of 83.45% and flux of 214μg/cm²/hr and permeability coefficient of 0.010 cm²/hr was obtained for metered dose topical spray formulation S3 containing Eudragit RLPO at 2.5% w/w concentration. Also the films formed were transparent, non-tacky, not blowing, spherical spray pattern and fast drying. Hence formulation S3 was considered for further optimization.

3.2.4 Effect of Plasticizers:

A series of formulations were prepared to study the effect of different plasticizers on various properties of metered dose topical spray formulations. Plasticizers such as PEG 400, Propylene glycol and Dibutyl phthalate were explored for the formation of a breathable, flexible, transparent film when Eudragit RLPO was used as film forming polymer. Propylene glycol used at concentration of 0.25% and 0.5% gave higher flexibility to the film compared to other plasticizers used at varying concentrations. Higher amount of drug permeated (84.42%) and flux (216μg/cm²/hr) and permeability coefficient (0.0108 cm/hr) were observed in formulation, F17 consisting of Propylene glycol 0.25%.
3.2.5 Effect of permeation enhancers

Menthol, Camphor and Transcutol P were incorporated as penetration enhancers at 0.5% w/w concentration in the formulations of Dexibuprofen metered dose topical sprays. They were freely soluble in solvent system used in the spray formulation. It can be seen that there was no significant difference in the results obtained with different penetration enhancers used and menthol exhibited the highest flux of 240.98 μg/cm²/hr and drug permeation of 99.6% amongst all. Menthol showed significant increase in flux and hence was used in the concentration of 0.5% in the optimized MDTS of Dexibuprofen 10%.

3.3 Evaluation of the optimized metered dose topical spray of Dexibuprofen:

*in-vitro and ex-vivo* permeation studies of the optimized batch, S19:

*In-vitro* permeation studies for optimized formulation, S19 was studied on Franz Diffusion cell using Dialysis membrane 150. The % drug permeated at the end of 24 hours was found to be 99.6%.
Fig.4: **in-vitro** permeation profile of optimized MDTS Formulation, F19.

The ex vivo drug permeation for formulation F19 was studied using porcine ear skin. The ex vivo profile indicated that the drug diffusion from the formulation F19 was 98.94% at the end of 24 hours which showed prolonged drug release.

Fig.5: **Ex vivo** permeation profile of optimized MDTS Formulation, F19.

Metered dose topical spray formulation, S19 exhibiting optimal in vitro and ex vivo drug transport profile was selected and evaluated for the various physicochemical parameters: The pH of formulated batches ranged from 6.0 to 6.7. The pH of human skin is in between pH 5.5 and 6.5. Hence, the pH adjustment was unnecessary. The viscosity of the optimized Dexibuprofen metered dose topical spray was found to be 25.2 cps (± 2.5cps). The volume of solution delivered upon each actuation was 110μl ±0.05 μl. Spray angle was found to be 54.46° ± 0.4°(n=3) and spherical spray pattern was observed. The results obtained were reproducible. Formulated batches showed good sprayability. The % drug content of the optimized formulation was found to be in the acceptable range of101.2% ± 0.5 for n=3. The drug content per spray was found to be 11±0.05 mg. The optimized formulation (S19) of Dexibuprofen containing Eudragit® RLPO yielded flexible films on the human skin. Ex–in vivo film formation test passed the desired criteria of film formation, which varied from 50 s to 70 s after actuation. Feeling of warmth and subsequent cooling sensation were perceived after application of spray.
(around 10 min) because of menthol in the formulation. Dermal adhesion and flexibility of films were good. The films could be easily washed off with water with slight rubbing.

Fig.6: Appearance of Film formed on actuation from MDTS container (S19)

3.4 Stability Studies:

Stability of metered dose topical sprays was assessed by evaluating the physicochemical parameters of formulations stored at different temp and humidity conditions over a period of three months and was found to be satisfactory till the end of three months. It can be concluded that there were no signs of drug degradation and the drug was present uniformly distributed throughout the storage period. There was no significant change in pH of drug formulation indicating no degradation during storage. Uniform spray pattern was observed during the entire period and there was no colour change indicating that there may be no interaction of the formulation with the components of metered dose spray containers.

A: Spray pattern which is not acceptable

B: Spray pattern by APF Plus pumps from Aptar Pharma

C: Spray pattern by Local vendor

Fig.7 Spray pattern
3.5 Preclinical Studies:

3.5.1 Carageenan induced paw edema method:

Significant inhibition of paw edema was observed for the formulation till the 24\textsuperscript{th} hour. The anti-inflammatory activity of Dexibuprofen polymeric film forming topical spray was compared with commercial Volini spray. Polymeric film forming topical sprays showed comparable inhibition of paw edema with respect to marketed formulation. Conventional Volini spray (group II) showed maximum inhibition of 41.01\% at 4\textsuperscript{th} hr. Group III (i.e. polymeric film forming topical spray, S19) showed maximum inhibition of 46.78\% at 6\textsuperscript{th} hr.

Fig. 8: Comparative Percent Inhibition at various time intervals

3.5.2 Antinociceptive Activity Using Hot Plate Analgesiometer

From the hot plate test it was revealed that the formulation showed a better efficacy in pain inhibition as compared to the Placebo or negative control. The onset of analgesia was rapid, with peak effects seen at 4 h followed by decrease in the response at the end of 8 h. Dexibuprofen was effective topically in the hot-plate assay achieving a maximal response at the
end of 4 h and % MPE calculated was 56.63 % for Dexibuprofen polymeric metered dose topical spray, S19.

The P ≤ 0.05 were considered as statistically significant. Compared to the negative control the test formulations showed a much higher latency period (P ≤ 0.05). Comparisons between the test formulations evaluated and the marketed formulations indicated that there is significant difference between the pain inhibitions for film forming spray at the fourth hour where the pain inhibition capacity is higher than that of the conventional spray as observed.

The inhibition of pain perception was sustained over 8 hours, which corroborates with the results observed in the ex-vivo drug diffusion studies where the drug was diffused over a period of 8 hours and showed prolonged delivery.

3.5.3 Skin irritation test:

Photograph of intact rat skin treated after application of spray formulations with placebo spray

Fig.10: Spray application

Fig.11: Placebo spray

Fig.12: 24 hours after Spray application

Fig.13: 72 hours after Spray application
The negative control (placebo spray) and the test formulation did not show any erythema or edema in all the three rats at the end of 24 hours and 72 hours. The Primary Irritation Index (P.I.I.) was found to be 0.00 for the polymeric film forming topical spray formulations of Dexibuprofen. Therefore, the developed formulation is considered as non-irritant and safe for topical use.

4. CONCLUSION:

The MDTS has the potential to offer enhanced passive topical drug delivery system with little or no skin irritation primarily as a result of its non-occlusive nature and the skin tolerability. The method of preparation of metered dose topical sprays was simple and formulation offered advantages of lower skin irritation, greater ease of use and increased dosage flexibility. The developed topical formulations were transparent, non greasy and aesthetic in appearance. The product is more convenient to use, since it is into compact unit and can be applied easily and quickly. Use of propellants was eliminated as to reduce the hazard of handling propellants at pressure and their cost. Metered-dose topical spray has the potential to expand the growth of TDD systems by broadening patient acceptance and pharmaceutical applications for enhanced TDD.

5. ACKNOWLEDGEMENTS:

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6. REFERENCES:


